Effects of Nicotine on Spinal Cord Injury Pain: A Randomized, Double-Blind, Placebo Controlled Crossover Trial

Elizabeth J. Richardson, PhD,[1] J. Scott Richards, PhD,[1]
Christopher C. Stewart, PhD,[2] and Timothy J. Ness, MD, PhD[3]

[1]Department of Physical Medicine and Rehabilitation, University of Alabama at Birmingham, Birmingham, Alabama; [2]Department of Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin; [3]Department of Anesthesiology, University of Alabama at Birmingham, Birmingham, Alabama

Background: One factor affecting spinal cord injury (SCI)–related pain may be nicotine. Case reports have described a worsening of neuropathic pain from smoking and relief from abstinence. Neurobiological correlates also implicate the potential effect of nicotine on SCI-related pain. **Method:** The current study employed a randomized, placebo-controlled crossover design to examine the effect of nicotine exposure on subtypes of SCI-related pain among smokers and nonsmokers. **Results:** Whereas nonsmokers with SCI showed a reduction in mixed forms of pain following nicotine exposure, smokers with SCI showed a converse increase in pain with regard to both mixed and neuropathic forms of pain. The exacerbation of pain in chronic nicotine or tobacco users may not only elucidate possible pain mechanisms but may also be of use in smoking cessation counseling among those with SCI. **Key words:** *neuropathic pain, nicotine, pain, smoking, spinal cord injury, randomized controlled trial*

Approximately 70% of persons with spinal cord injury (SCI) report pain, with a third of those individuals describing the pain as severe.[1] Pain following SCI leads to significant disruptions in mood and psychosocial functioning,[2,3] occupational activities,[4] and basic needs such as sleep.[5,6] Among other complications of SCI, pain has consistently been associated with lower quality of life.[7-9] Current treatments targeting pain after SCI remain relatively inadequate.[10] Development of therapeutic interventions most often follow from laboratory discoveries, which lead to trials for efficacy in clinical settings. However, the reverse can be true as well: attention to clinical observations of factors associated with both pain exacerbation and relief can help drive the agenda at the "workbench." Important clinical observations, when well controlled, may lead to increased understanding of mechanisms and more effective treatments.

One such clinical observation is exacerbation of pain by smoking, a phenomenon noted over a half century ago[11,12] that has subsequently received little attention. In recent years, however, interest in a possible relationship between pain and smoking has reemerged. Increased levels of musculoskeletal pain in the limbs and backs of non-SCI persons have been associated with smoking.[13,14] Among persons with SCI, similar findings have emerged, as results from one longitudinal study found that those who were smokers with SCI reported more musculoskeletal pain across time.[15]

Case reports also suggest that smoking affects a particular subtype of SCI-related pain: neuropathic pain. Richards and colleagues[16] noted 2 individuals with SCI who experienced worsening of neuropathic pain from smoking. Two men with long-standing paraplegia were habitual smokers of ½ to 1 pack of cigarettes per day. When required to stop smoking prior to a surgical procedure to repair nonhealing pressure sores, the men complied and subsequently reported a marked reduction in pain levels. After discharge, both men resumed smoking and reported an immediate return of the pain to the level experienced prior to their abstinence.

Although evidence to date suggests a relationship between smoking status and pain exacerbation following SCI, available data are descriptive/correlational and therefore cannot be used to infer causal relationships. Moreover, SCI-related pain

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in most studies has typically been assessed in a generalized manner, yet pain following SCI is not a unitary phenomenon. Therefore, the purpose of this study was to examine, via a randomized, placebo-controlled crossover trial, the effects of nicotine on various specific subtypes of pain following SCI.

Methods

Participants

Forty-two persons with SCI participated in the current study. Demographic composition was as follows: (a) 20 Caucasians and 22 African Americans, (b) 26 men and 16 women, (c) 14 persons with tetraplegia and 28 with paraplegia, and (d) 31 smokers and 11 nonsmokers. The mean age and duration of injury for the group were 43.9 years (range, 19-59) and 12.2 years (range, 0.5-32.5), respectively. All participants gave informed consent for the study as required by the University of Alabama at Birmingham Institutional Review Board.

Two interviewers, trained to criteria on the Bryce-Ragnarsson scheme,[17] simultaneously but independently classified up to 3 "worst" pain sites of each participant. We have used this methodology successfully in peer-reviewed studies of SCI pain classification schemes.[18-20] Classification of pain from each participant resulted in a sample size of 103 pain sites. Specifically, 42, 39, and 20 pain sites were categorized as musculoskeletal (MS), neuropathic (NP), and mixed pain (MX), respectively. Two pain sites were classified as visceral pain, but were not included in the final analyses.

Procedures

Smokers were asked to refrain from smoking on the day of testing. On 2 separate occasions, participants were presented a sequence of gum stimuli involving nicotine gum or placebo gum. Each sequence, or trial, was conducted approximately 1 week apart. During each trial arm, participants were given 1 mg nicotine gum (or placebo) in the first hour and 2 mg nicotine (or placebo) in the second hour. Order of trial arms was randomized to each participant. Heart rate and pain ratings were collected at 10-minute intervals over the 120-minute period in each arm. A 0-10 numeric rating scale (NRS) was used to rate pain. Ratings collected at 30 minutes post administration of dose for each hour were used in the analyses, because this time frame parallels time to peak nicotine blood plasma levels via nicotine gum.[21] Data were analyzed via repeated measures mixed analysis of covariance (ANCOVA) models, controlling for average pain ratings for 24 hours preceding testing.

Results

Mean heart rate remained elevated across time in the nicotine condition as compared to placebo (**Figure 1**). **Figure 2** shows responses of smokers and nonsmokers in each trial across treatment dosages and pain type. In the placebo arm, significant main effects for both smoking, $F(1, 86) = 11.216$, $P = .001$, and pain type, $F(2, 86) = 3.265$, $P = .043$, emerged. In the nicotine arm, there was a significant Smoking x Pain (across dosage) interaction, $F(1, 86) = 11.030$, $P = .001$, and a Pain Type x Smoking interaction, $F(2, 86) = 4.647$, $P = .012$, indicating increased MS and NP and no change in MS pain among smokers and a decrease in MX pain for nonsmokers.

Discussion

Although not robust, these findings suggest differential effects on SCI-related pain for smokers and nonsmokers. Reduced MX pain among nonsmokers is consistent with the previously identified analgesic effects of nicotinic agonists.[22] However, smokers appeared to experience an effect to the contrary in that pain sites with a neuropathic component (MX and NP) worsened with nicotine exposure. This is similar to results from animal models indicating that nicotine-induced analgesia is relatively an acute effect that minimizes with chronic nicotine exposure.[23-25] Further, exposure to nicotine exerts pro-excitatory actions on primary afferent neurons and dorsal horn neurons[26-28] and sensitizes TRPV1 receptor channels.[29,30] This suggests that chronic nicotine exposure, as occurs with habitual

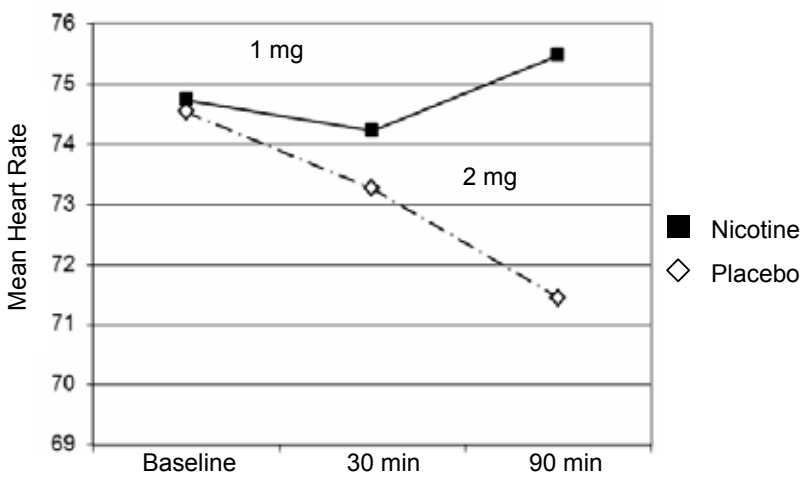

Figure 1. Mean heart rate for all participants across conditions.

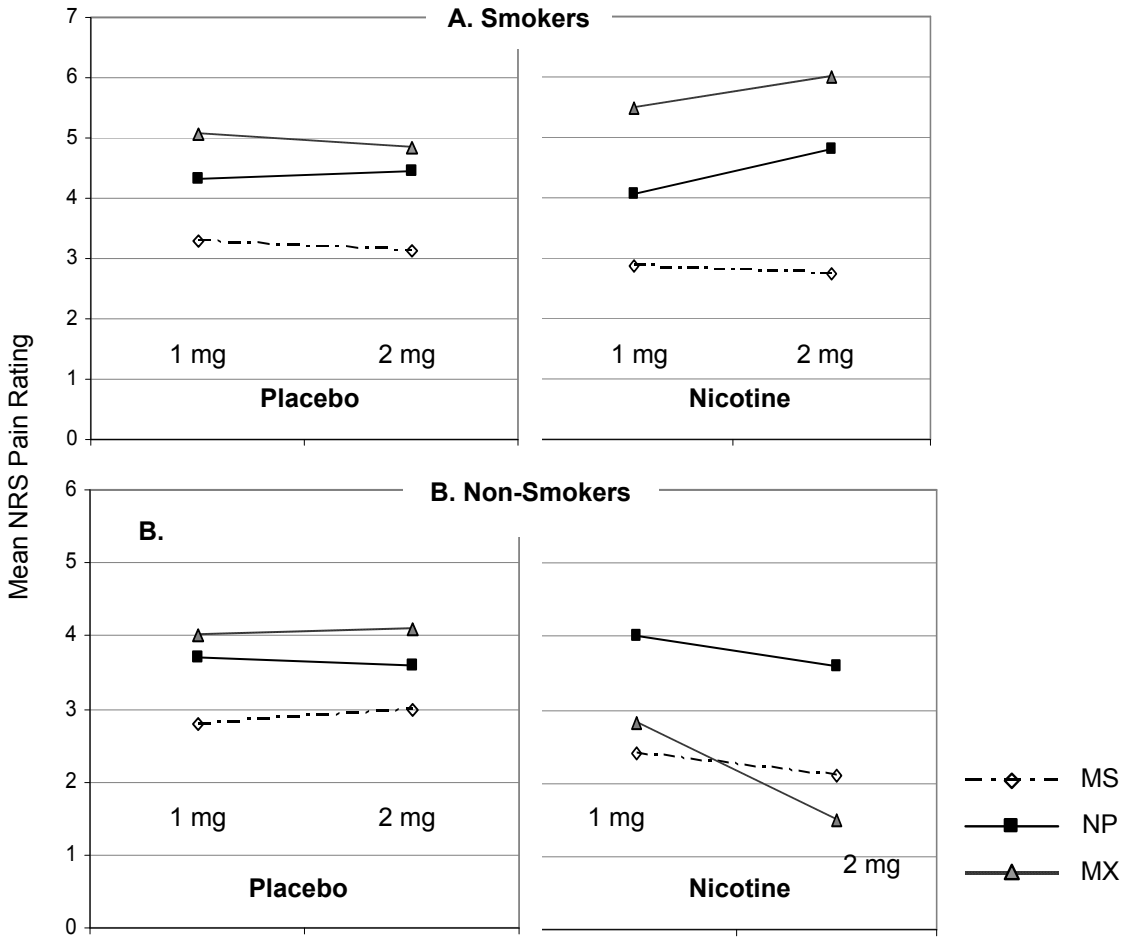

Figure 2. Graphs are as follows: (A) pain ratings across conditions for smokers with SCI and (B) pain ratings across conditions for nonsmokers. Data points for 1 mg and 2 mg of nicotine correspond to 30-minute and 90-minute pain ratings for each condition, respectively. MS = musculoskeletal pain; NP = neuropathic pain; MX = mixed pain.

smokers or tobacco users, may alter the structural, functional, and potentially the biochemical integrity of nociceptive pathways. Consequently, smoking or tobacco use would determine the analgesic (or enhanced nociceptive) effect.

These findings, in conjunction with prior clinical observations[11,12,16] and neurobiological evidence implicating possible mechanisms of pain in the context of nicotine use, suggest a potentially fruitful area of future research in both human and animal studies. In addition, the results found among smokers could lead to targeted interventions based on mechanisms underlying the nicotine-pain connection. Further understanding regarding the effects of smoking on pain may also prompt behavioral interventions, such as individual and/or group smoking cessation programs.

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